

524149

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



11 FEB 2005

(43) International Publication Date
26 February 2004 (26.02.2004)

PCT

(10) International Publication Number
WO 2004/016633 A1

- (51) International Patent Classification⁷: **C07H 17/00**, **A61K 31/70**
- (21) International Application Number: **PCT/GB2003/003562**
- (22) International Filing Date: 14 August 2003 (14.08.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0218811.8 14 August 2002 (14.08.2002) GB
- (71) Applicant (for all designated States except US): **CENES LIMITED** [GB/GB]; Compass House, Vision Park, Chivers Way, Histon, Cambridge CB4 9ZR (GB).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **GRAHAM, John, Aitken** [GB/GB]; CeNeS Limited, Compass House, Vision Park, Chivers Way, Histon, Cambridge CB4 9ZR (GB).
- (74) Agent: **DAVIES, Jonathan, Mark**; Reddie & Grose, 16 Theobalds Road, London WC1X 8PL (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
- with international search report
 - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SALT OF MORPHINE-6-GLUCURONIDE

(57) Abstract: The hydrobromide salt of morphine-6- β -D-glucuronide (M6G.HBr) is surprisingly stable compared to other M6G salts and M6G base. Use of M6G.HBr as a medicament, in particular as an analgesic, and methods of making M6G.HBr are described.

WO 2004/016633 A1

Salt of Morphine-6-Glucuronide

This invention relates to a salt of morphine-6- β -D-glucuronide (M6G; see Figure 1) with improved stability, and to use of the salt as a medicament, in particular as an analgesic.

M6G is a metabolite of morphine which is known to be a more powerful analgesic than morphine itself and yet has fewer side effects. Methods of preparation of M6G are described in WO 93/03051, WO 93/05057, WO 99/58545 and WO 99/38876.

Whilst M6G base is stable when stored at -20°C , it does degrade when stored at room temperature. This degradation is not only noted by an increase in detectable degradation products, but also by a marked colour change of the compound. This will limit the shelf life of M6G base at ambient temperature.

It has now been found that the hydrobromide salt of M6G (M6G.HBr) is surprisingly stable compared to M6G base and other M6G salts, in particular the hydrochloride (M6G.HCl) and sulphate (M6G $_2$.H $_2$ SO $_4$) salts. M6G.HBr showed a very limited amount of degradation and no discolouration after storage at room temperature for six years (see Example 1 below).

According to the invention there is provided a hydrobromide salt of M6G (M6G.HBr). Methods of preparation of M6G.HBr are described in Examples 2 and 3 below.

M6G.HBr may be used as a medicament, in particular as an analgesic. Examples are for the treatment of moderate to severe, acute and chronic nociceptive pain (such as post-operative pain, pain associated with malignant and non-malignant diseases), and neuropathic pain.

M6G.HBr may be administered by any suitable route. Examples are as a solid formulation (e.g. for oral, dry powder inhalation), as a solution formulation (e.g. intravenous (including infusion for

PCA), subcutaneous, intranasal, or sublingual), or as a transdermal formulation (e.g. by simple diffusion or by enhanced electrophoretic methods). Transdermal administration of pharmaceutically acceptable acid addition salts of M6G is described in US 5,705,186.

According to the invention there is also provided a pharmaceutical composition comprising an analgesically effective amount of M6G.HBr together with a pharmaceutically acceptable carrier, excipient, or diluent.

An analgesically effective amount of M6G.HBr will vary with the route of administration, and with factors such as the age, sex, weight, and condition of the subject being administered, and with the type of condition being treated. In general, a suitable dose for an acute condition will be lower than for a chronic condition.

A suitable dose is in the range of 1-1000mg/70Kg, preferably 1-200mg/70Kg, more preferably in the range of 5-75mg/70Kg. A preferred dose for acute use is in the range of 5-75mg/70Kg. A preferred dose for chronic use is in the range of 30-500mg/kg. Dosage for routes of administration where bio-availability is high (e.g. intravenous, subcutaneous, intranasal, sublingual) will be lower than for routes with low bio-availability (e.g. oral).

M6G.HBr may also be used for the symptomatic treatment of breathlessness in patients with advanced cancer. Any suitable route of administration may be used, but a preferred route is inhalation of nebulized M6G.HBr. The effect of administration of nebulized M6G is described by Quigley et al (in *J. Pain Symptom Manage.*, Letters, Vol 23, No.1 (2002), pages 7-9). A dosage of M6G.HBr effective for the treatment of breathlessness in a subject with advanced cancer will vary with the route of administration, and with factors such as the age, sex, weight, and condition of the subject being administered. A suitable dose

is in the range of 1-200mg/70Kg, preferably in the range of 5-75mg/70Kg.

There is further provided according to the invention a method of making M6G.HBr which comprises: (i) contacting a hydrogen bromide solution with a solution of M6G in methanol; (ii) contacting the solution resulting from step (i) with an organic solvent to precipitate M6G.HBr; and (iii) isolating M6G.HBr precipitated in step (ii).

Preferably the solutions and solvent are at -15°C, or below. This minimises formation of degradation products.

Preferably the precipitated M6G.HBr is washed to minimise the amount of organic solvent present. For example, the precipitated M6G.HBr may be washed with diethyl ether.

A preferred organic solvent is 2-propanol.

According to a preferred method a cooled diluted solution of HBr is added to a continuously stirred, cooled (to at least -15°C) solution of M6G in methanol. Then 2-propanol (or other suitable organic solvent) is added, and the resulting suspension is maintained below -15°C, while continuously stirring. Following stirring of the suspension the resultant crystals are filtered and washed with a suitable solvent (e.g. 2-propanol or diethyl ether) and dried by suitable means (e.g. under vacuum at room temperature).

The following examples 1 and 2 relate to the stability of M6G salts at room temperature, and methods of preparation of M6G salts, respectively. Table 1 shows the stability data for the M6G salts tested, and Figure 1 shows the chemical structure of M6G and identified degradants. Example 3 relates to the stability of M6G salts and base at 25°C/60%RH, 40°C/75%RH and 60°C. Tables 2-4 show the data relating to example 3.

Example 1 Stability of M6G salts at room temperature over 6 yearsAnalytical investigation by HPLC:

Samples of the hydrochloride salt (M6G.HCl) (205-2056), the sulphate salt (M6G₂.H₂SO₄) (205-2060), and the hydrobromide salt (M6G.HBr) (205-2059) of M6G were stored at room temperature for almost 6 years and then analysed by HPLC. The results are shown in Table 1, together with the results of HPLC analysis of samples prepared under similar conditions a few months earlier.

Results:

M6G.HCl (205-2056): The content of M6G decreased to 69% (starting from ~82%). HN-67002 and HN-67003 (which are typically oxidation products) increased to 1.3% and 2.1% respectively. The content of HN-33177, a synthetic impurity of M6G, remained unchanged. However, there are 17 peaks present in the chromatogram that cannot be identified by retention time. The total of these impurities is 9.2 area %.

M6G₂.H₂SO₄ (205-2060): The content of M6G decreased to 63% (starting from ~77%). HN-67002 and HN-67003 increased to 1.1% and 1.8% respectively. The content of HN-33177 did not change. However, there are 13 peaks present in the chromatogram that cannot be identified by retention time. The total of these impurities is 10.7 area % with a dominant peak at 23.5 min (6.55 area %).

M6G.HBr (205-2059): The content of M6G did not decrease at all and the content of HN-67002 (0.5%) and HN-67003 (0.2%) is much lower than in the samples discussed above. There are only 4 additional peaks present in the chromatogram. None of these are bigger than 0.4 area %. The result is superior to the two other salts tested.

Conclusion:

The hydrobromide salt of M6G shows very limited degradation and was not discoloured after storage for six years at room temperature compared to the free base and other salts

investigated. Thus, the hydrobromide salt of M6G has improved stability at room temperature compared to the hydrochloride and sulphate salts of M6G.

5 Example 2 Preparation of hydrobromide and sulphate salts of M6G

Preparation of Q 3196 (M6G.HBr, 304-4428):

4.99g of M6G.2H₂O were dissolved in 11ml of Methanol and cooled to -15°C. 1.16ml of HBr (48% in water) was diluted with 0.85ml
10 of Methanol and cooled to -15°C and added slowly to the solution of M6G. A clear, highly viscous, pale yellow solution was obtained. The solution was stirred for 5 minutes before 100ml 2-propanol (-15°C) were added. The product precipitated immediately. The slurry was stirred for 3.5 hours at -20°C, the
15 crystals were filtered off, washed with 37.5ml cold 2-propanol (-20°C) and dried at room temperature in a high vacuum. The yield was 5.61g.

Preparation of Q 3195 (M6G₂.H₂SO₄, 304-4429):

20 5.02g of M6G.2H₂O were dissolved in 11ml of Methanol and cooled to -15°C. 0.35ml of H₂SO₄ (96%) was diluted with 0.85ml of Methanol and cooled to -15°C and added slowly to the solution of M6G. A clear, highly viscous, pale yellow solution was obtained. The solution was stirred for 5 minutes before 100ml 2-propanol (-
25 15°C) were added. The product precipitated immediately. The slurry was stirred for 3.5 hours at -20°C, the crystals were filtered off, washed with 37.5ml cold 2-propanol (-20°C) and dried at room temperature in a high vacuum. The yield was 5.36g.

30 Example 3 Stability of M6G salts after 1 month at 60°C and 3 months at 25°C/60% relative humidity and 40°C/75% relative humidity

The analytical data below gives clear evidence that the stability
35 of the hydrobromide salt is superior to all other salts assessed and in addition would appear to be more stable than Morphine-6-glucuronide base. The data demonstrates that the hydrobromide

salt is stable when subjected to storage conditions of 25°C/60%RH and 40°C/75%RH for 3 months and 60°C for 1 month. The base appears to be relatively stable to storage conditions of 25°C/60%RH after three months, but shows signs of degradation at
5 40°C/75%RH over 3 months and 60°C over 1 month.

All of the other salts show some form of degradation at 25°C/60%RH and at elevated temperature and humidity.

10 The Morphine-6-glucuronide sulphate salt is the least stable at 25°C/60%RH, whilst the Morphine-6-glucuronide hydrochloride is the least stable at 40°C/75%RH as this shows the greatest level of degradation of all the salts.

15 Introduction

Various salts and the base of Morphine-6-glucuronide have been subjected to storage conditions of 25°C/60%RH and 40°C/75%RH for 3 months and 60°C for 1 month.

20 The analytical testing comprised of:

- Visual appearance
- Water content (%w/w) by Karl Fisher analysis
- Assay (% w/w) and related substances determination
- 25 • Colour of solution by UV spectrophotometry.

The results obtained for each test were used to assess the stability of the various salts and the base.

30 Experimental procedures

Materials

Test Item Characterization, Sample Description

35 Six different salts of morphine-6-glucuronide were prepared from morphine-6-glucuronide base; the hydrobromide (HBr), sulphate (H₂SO₄), phosphate (H₃PO₄), hydrochloride (HCl), fumarate and maleate. The HBr salt was prepared by the method described in Example 2. The only difference was that after the 2-propanol slurry was filtered, the solid

was then washed three times with diethyl ether, before drying under vacuum at room temperature. This additional step was employed to remove as much 2-propanol from the salt as possible.

- 5 The other inorganic salts (sulphate, phosphate, hydrochloride) were prepared in a similar way, i.e. by addition of the relevant acid to a cooled stirring suspension of morphine-6-glucuronide base in methanol, trituration of the resultant solution with cooled 2-propanol to form a suspension, and then continuous stirring at low temperature. Filtration
10 of the solid is followed by washing with diethyl ether, and then drying at room temperature under reduced pressure.

The maleate and fumarate were prepared by the addition of the desired acid, on stirring at room temperature, to an aqueous solution of
15 morphine-6-glucuronide base until all material was dissolved. The solution was then freeze dried to produce the required solid.

The same batch of morphine-6-glucuronide base (Batch M01003) was used to prepare each salt. This batch had been synthesised and tested to confirm
20 identity, chemical and microbiological purity.

All salts prepared were tested to confirm appearance, assay (%w/w) by HPLC, confirmation of presence of correct counter ion, water content (%w/w) by Karl Fisher analysis, residual solvent analysis by GC and
25 determination of colour of solution by measurement of UV absorbance of a 5 %w/v solution at 420 nm.

Description of Salts of Morphine-6-glucuronide:

30

Description	Molecular Weight	Batch Number
M6G Hydrobromide salt M6G.HBr	542.37	JCCA24B
M6G Sulphate salt (M6G) ₂ .H ₂ SO ₄	1021.00	JCCA25B
M6G Phosphate salt M6G.H ₃ PO ₄	559.46	JCCA26B
M6G Fumarate salt (M6G) ₂ Fumarate	1039.00	MM13A
M6G Maleate salt (M6G) ₂ Maleate	1039.00	MM14A
M6G Hydrochloride salt M6G.HCl	497.92	MM10C

Description of Reference substances used in Testing of Salts:

Reference substance	Description	Batch number
HN-33169	M6G	401-2055
HN-33177	Synthetic impurity	401-2052
HN-75083	Degradant	401-2054
HN-75076	Degradant	401-2044
HN-67003	Degradant	401-2058
Morphine sulphate pentahydrate	Degradant	40IK1192

5 Each test material was stored between 2-8°C prior to placing on stability. Each material was sub-divided into 900mg aliquots, transferred to brown opaque HDPE plastic bottles and flushed with Argon prior to sealing. Sufficient samples were provided for each time point as well as spares for each storage condition. The
 10 samples were placed in appropriate incubators previously commissioned at storage conditions 25°C/60%RH, 40°C/75%RH and 60°C.

The reference materials were stored under secure conditions at
 15 -20°C or below until required for testing.

Methods

The samples were stored for analysis according to the following
 20 table:

Storage Condition	Initials	1 month	3 months
25°C/60% RH	X	X	X
40°C/75%RH		X	X
60°C		X	-

X = Appearance, Water content by Karl Fischer analysis, Assay and Related Substances and Colour by UV /Vis spectrophotometry.

25

Testing ProceduresTest for identity Content and Impurities

Testing was performed in duplicate (2 x 25mg) in accordance with

a stability indicating HPLC assay method. The assay results were reported as M6G as is, M6G as the anhydrous, solvent free material and the anhydrous solvent free material corrected for the salt form using the relevant conversion factor.

5

Water Content by Karl Fisher Analysis

Water content was determined in duplicate on an aliquot of equilibrated material (approximately 100 mg) using a Tritrino 720 KFS Titrator.

10

Colour by Visible Spectrophotometry

A 5% w/v solution of test material was prepared in water and the absorbance measured at 420nm in a 1cm silica cell using a Unicam UV4 Visible/UV spectrophotometer.

15

Results

These are shown in Tables 2-4.

20

Discussion

On storage for 3 months at 25°C/60%RH the hydrobromide, hydrochloride, phosphate and base remain as white crystalline solids, the other salts showing varying degrees of colouration. However on storage at 40°C/75%RH over the same period, all the salts (except the hydrobromide) plus the base show signs of becoming yellow in appearance. The change in appearance is reflected in the results for colour of solution, which increases in value as the yellow colour of the solid becomes more intense.

30

The general trend in moisture content is that the higher the storage humidity the greater the moisture content of the samples. The exception however is the base, where the moisture content is reasonably consistent regardless of storage condition. Of the salts the largest change in moisture content is with the

35

phosphate (increase of around 8% at 40°C/75%RH compared to initial).

Review of the 3 month assay data shows some interesting trends.

5 The most stable materials (based on %w/w assay) are the hydrobromide, base and phosphate. It should be noted that the reason that the phosphate assay values are high throughout the study (around 110%± 5%), is that there were some problems in the preparation of this salt. These issues resulted in the material
10 being present as a mixture of phosphate/base in a ratio of approximately 10.8:1. The maleate and fumarate show a drop in assay of around 10% after 3 months at 40°C/75%RH compared to the initial values. Interestingly the hydrochloride shows a small decrease in assay after 3 months storage at 25°C/60%RH (around 6%
15 compared to initial), however a dramatic reduction at 3 months storage at 40°C/75%RH (approx 34% decrease compared to initial). This reduction is in fact more than that seen with the sulphate salt, which from the 1-month data alone was thought to be the most unstable salt. The low assay value seen at 3months
20 40°C/75%RH, may be linked to the breakdown of the crystal form at high humidity resulting in a high degree of degradation. This degradation is reflected in the amount of degradation products seen in this sample (total of around 54.5%)

25 Even after 3 months storage at 40°C/75%RH there is basically no increase in the amount of degradation products in the hydrobromide salt as measured by HPLC. At the same conditions, there is an increase of approximately 3% in the amount of degradation products in the base. The levels of degradation are
30 similar for the fumarate and maleate, slightly less for the phosphate. The least stable salts are the sulphate and the hydrochloride, with some indication that the hydrochloride is more stable than the sulphate at 25°C/60%RH, but the reverse being the case at 40°C/75%RH.

Conclusion

The results obtained indicate that the hydrobromide salt appears more stable than all other salts and the base. An overall review
5 of the data suggests the following order of stability:

Hydrobromide>base>>phosphate/maleate/fumarate>sulphate/hydrochloride

Table 1: Stability Data of M6G-Salts Stored at Ambient Temperature in Example 1

Salt	Batch	Elapsed Time (years)	Assay M6G uncorr.	Assay M6G corr.	HN-67002	HN-75076	Morphine	HN-75083	HN-67003	HN-33177	Unknown related substances (sum area %)
Hydrochloride	205-2042	0	82.2	88.7	---	n.d.	n.d.	< 0.1	---	0.3	<0.1
	205-2056	6	69.3	74.8	1.3	n.d.	0.2	n.d.	2.1	0.2	9.2
Sulphate	205-2041	0	77.2	93.6	---	n.d.	n.d.	< 0.1	---	0.2	0.2
	205-2060	6	63.3	76.8	1.1	n.d.	0.2	n.d.	1.8	0.3	10.7
Hydrobromide	205-2045	0	77.2	90.7	---	n.d.	n.d.	< 0.1	---	0.3	< 0.1
	205-2059	6	81.9	96.3	0.5	n.d.	n.d.	n.d.	0.2	0.4	1.0
Free base	F12061	0	N/A	98.2	n.d.	n.d.	n.d.	n.d.	n.d.	0.7	<0.1
	F12061	5	N/A	81.2	n.d.	n.d.	0.3	n.d.	n.d.	0.8	11.8

n.d. not detectable

--- not investigated

- 5 M6G uncorr. content calculated as M6G base
M6G corr. content calculated as M6G derivative = M6G uncorr. x f
f = molecular weight (M6G-derivative) / molecular weight (M6G)

Table 2
Appearance, Moisture and Colour by Visible spectrophotometry: Example 3

Designation	Reference	Time (months)	Storage (°C/60%RH)	Appearance	Moisture (g/g)	Colour (Absorbance)
Morphine-6-glucuronide sulphate	299615	Initial		White crystalline powder	3.77	0.136
	307571	1 month	25°C/60%RH	White crystalline powder	4.28	0.244
	318587	3 months		Pale yellow crystalline powder	5.54	0.406
	307578	1 month	40°C/75%RH	Slightly yellow crystalline powder	5.93	0.430
	318594	3 months		Slightly yellow crystalline powder	8.31	1.056
	307585	1 month	60°C	Pale yellow crystalline powder	4.68	1.714
Morphine-6-glucuronide hydrobromide	299616	Initial		White crystalline powder	2.38	0.029
	307570	1 month	25°C/60%RH	White crystalline powder	2.56	0.073
	318588	3 months		White crystalline powder	3.28	0.046
	307577	1 month	40°C/75%RH	White crystalline powder	3.19	0.064
	318595	3 months		White crystalline powder	4.24	0.066
	307584	1 month	60°C	White crystalline powder	1.95	0.261
Morphine-6-glucuronide hydrochloride	299617	Initial		White crystalline powder	4.31	0.059
	307565	1 month	25°C/60%RH	White crystalline powder	5.10	0.147
	318589	3 months		White crystalline powder	6.06	0.253
	307572	1 month	40°C/75%RH	Slightly yellow crystalline powder	6.24	0.444
	318596	3 months		Yellow crystalline powder	9.02	2.107
	307579	1 month	60°C	Pale yellow crystalline powder	4.44	1.183

continued

Table 2 (continued)

Designation	Laboratory Reference	Time Point	Storage Condition	Appearance	Moisture (%)	Colour (Abs @ 420nm)
Morphine-6-glucuronide fumarate	299618	Initial		White crystalline powder	6.80	0.016
	307569	1 month	25°C/60%RH	White crystalline powder	7.26	0.034
	318590	3 months		Pale yellow crystalline powder	8.00	0.141
	307576	1 month	40°C/75%RH	Pale yellow crystalline powder	7.94	0.264
	318597	3 months		Yellow crystalline powder	10.89	1.008
	307583	1 month	60°C	Yellow crystalline powder	5.98	0.794
Morphine-6-glucuronide maleate	299619	Initial		White crystalline powder	6.14	0.017
	307568	1 month	25°C/60%RH	White crystalline powder	7.53	0.084
	318591	3 months		Pale yellow crystalline powder	7.14	0.209
	307575	1 month	40°C/75%RH	Pale yellow crystalline powder	7.60	0.297
	318598	3 months		Yellow crystalline powder	9.24	0.879
	307582	1 month	60°C	Yellow crystalline powder	5.01	0.739

continued

Table 2 (continued)

Patent No.	Patent No.	Time Point	Storage Condition	Appearance	Yield (%)	Color (Abs @ 420nm)
Morphine-6-glucuronide phosphate	299620	Initial		White crystalline powder	3.12	0.034
	307567	1 month	25°C/60%RH	White crystalline powder	3.91	0.053
	318592	3 months		White crystalline powder	5.06	0.098
	307574	1 month	40°C/75%RH	Slightly yellow crystalline powder	9.28	0.308
	318599	3 months		Slightly yellow crystalline powder	11.88	0.878
	307581	1 month	60°C	Pale yellow crystalline powder	5.12	0.787
Morphine-6-glucuronide base	299622	Initial		White crystalline powder	9.80	0.017
	307566	1 month	25°C/60%RH	White crystalline powder	9.00	0.040
	318593	3 months		White crystalline powder	9.53	0.132
	307573	1 month	40°C/75%RH	Pale yellow crystalline powder	9.68	0.182
	318600	3 months		Yellow crystalline powder	9.85	0.680
	307580	1 month	60°C	Yellow crystalline powder	8.21	0.541

Table 3
Assay: Example 3

Description	Laboratory Reference	Time Point	Storage Condition	Assay Basis	Atmospheric Basis	Corrected for Moisture
Morphine-6-glucuronide Sulphate	299615	Initial		80.62	88.49	97.87
	307571	1 month	25°C/60%RH	73.58	81.82	90.51
	318587	3 months		69.08	77.05	85.24
	307578	1 month	40°C/75%RH	65.04	73.67	81.50
	318594	3 months		59.39	68.38	75.64
	307585	1 month	60°C	57.15	63.84	70.62
Morphine-6-glucuronide hydrobromide	299616	Initial		82.26	83.63	98.29
	307570	1 month	25°C/60%RH	83.02	85.18	100.11
	318588	3 months		84.30	86.19	101.30
	307577	1 month	40°C/75%RH	82.40	85.09	100.01
	318595	3 months		83.14	85.85	100.90
	307584	1 month	60°C	82.82	84.44	99.25
Morphine-6-glucuronide hydrochloride	299617	Initial		81.63	93.28	100.65
	307565	1 month	25°C/60%RH	79.21	92.03	99.30
	318588	3 months		75.48	87.71	94.64
	307572	1 month	40°C/75%RH	69.13	81.39	87.81
	318595	3 months		51.00	61.41	66.26
	307579	1 month	60°C	65.73	75.78	81.76

continued

Table 3 (continued)

Designation	Reference	Time Point	Storage Condition	ASIS Index	Adhesions Index	Connective Tissue Index
Morphine-6-glucuronide fumarate	299618	Initial		84.11	89.44	100.71
	307569	1 month	25°C/60%RH	81.96	88.23	99.32
	318590	3 months		81.20	87.15	98.11
	307576	1 month	40°C/75%RH	77.62	84.17	94.76
	318597	3 months		71.64	79.38	89.37
	307583	1 month	60°C	77.33	82.11	92.44
Morphine-6-glucuronide Maleate	299619	Initial		83.61	88.28	99.40
	307568	1 month	25°C/60%RH	80.27	86.66	97.56
	318591	3 months		80.04	85.11	95.81
	307575	1 month	40°C/75%RH	77.07	83.28	93.75
	318598	3 months		72.37	78.73	88.63
	307582	1 month	60°C	76.46	80.36	90.47

continued

Table 3 (continued)

Description	Laboratory Reference	Time Point	Storage Condition	TIMG-ASSAY (2004)		
				At 15 days	At 10 days	Control Point
Morphine-6-glucuronide phosphate	299620	Initial		83.90	89.21	108.12
	307567	1 month	25°C/60%RH	84.57	91.37	110.76
	318592	3 months		84.25	91.16	110.50
	307574	1 month	40°C/75%RH	80.20	92.00	111.52
	318599	3 months		79.02	92.40	112.01
	307581	1 month	60°C	80.69	88.33	107.08
Morphine-6-glucuronide base	299622	Initial		91.07	99.79	99.79
	307566	1 month	25°C/60%RH	90.77	99.61	99.61
	318593	3 months		91.84	100.27	100.27
	307573	1 month	40°C/75%RH	89.94	99.45	99.45
	318600	3 months		88.67	97.15	97.15
	307580	1 month	60°C	89.31	96.18	96.18

Table 4
Related Substances: Example 3

Description	Laboratory Reference	Time Point	Storage Condition	Known Related Substances					Total Known	Total Unknown	Total Related Substances
				IN 20761	Morphine	IN 6003	IN 3177	IN 7593			
Morphine-6-glucuronide sulphate	299615	Initial		0.01	ND	0.15	0.69	0.23	1.08	0.64	1.72
	307571	1 month	25°C/60%RH	ND	ND	0.69	0.63	0.27	1.59	2.70	4.29
	318587	3 months		ND	0.17	1.36	0.52	0.53	2.58	6.58	9.16
	307578	1 month	40°C/75%RH	0.06	0.21	1.58	0.50	0.74	3.09	6.69	9.78
	318594	3 months		0.04	0.37	1.72	0.23	0.58	2.75	15.23	17.98
	307585	1 month	60°C	0.26	0.72	2.73	0.23	0.61	4.55	13.70	18.25
Morphine-6-glucuronide hydrobromide	299616	Initial		ND	ND	0.04	0.72	0.10	0.86	0.08	0.94
	307570	1 month	25°C/60%RH	ND	ND	ND	0.74	0.03	0.77	0.07	0.84
	318588	3 months		ND	ND	ND	0.77	0.04	0.81	0.12	0.93
	307577	1 month	40°C/75%RH	0.01	ND	ND	0.74	0.05	0.80	0.00	0.80
	318595	3 months		0.02	ND	ND	0.70	ND	0.72	0.00	0.72
	307584	1 month	60°C	0.04	ND	0.10	0.66	0.02	0.82	0.38	1.20
Morphine-6-glucuronide hydrochloride	299617	Initial		0.01	ND	0.07	0.63	0.06	0.77	0.47	1.24
	307565	1 month	25°C/60%RH	0.04	ND	0.38	0.63	0.03	1.08	1.33	2.41
	318588	3 months		ND	0.21	1.31	0.50	0.03	2.05	7.47	9.52
	307572	1 month	40°C/75%RH	0.34	0.08	3.01	0.41	0.07	3.91	11.25	15.16
	318595	3 months		1.67	1.55	3.71	0.07	0.01	7.01	51.57	58.58
	307579	1 month	60°C	0.55	0.46	3.55	0.12	0.03	4.71	16.23	20.94

continued

Table 4 (continued)

Designation	Laboratory Reference	Initial Point	Storage Condition	Known Related Substances (%)					Total Known Substances (%)	Total Unknown Substances (%)	Total Related Substances (%)
				HN75076	HN75077	HN75078	HN75079	HN75080			
Morphine-6- glucuronide fumarate	299618	Initial		ND	ND	0.04	0.77	0.05	0.86	0.09	0.95
	307569	1 month	25°C/60%RH	ND	ND	ND	0.80	0.03	0.83	0.08	0.91
	318590	3 months		ND	0.07	0.26	0.75	0.10	1.18	0.72	1.90
	307576	1 month	40°C/75%RH	0.03	0.10	0.58	0.70	0.02	1.43	1.17	2.60
	318597	3 months		0.40	0.45	1.56	0.57	ND	2.98	6.09	9.07
	307583	1 month	60°C	0.06	0.24	0.97	0.62	0.02	1.91	1.94	3.85
Morphine-6- glucuronide maleate	299619	Initial		ND	ND	0.04	0.76	0.05	0.85	0.00	0.85
	307568	1 month	25°C/60%RH	ND	ND	0.17	0.76	0.05	0.98	0.41	1.39
	318591	3 months		ND	0.04	0.58	0.52	0.06	1.20	2.35	3.55
	307575	1 month	40°C/75%RH	0.03	0.12	0.94	0.65	0.03	1.77	3.03	4.80
	318598	3 months		0.40	0.43	1.68	0.50	ND	3.01	6.93	9.94
	307582	1 month	60°C	0.14	0.32	1.20	0.50	0.02	2.18	3.91	6.09

continued

Table 4 (continued)

Identification of Substance	Laboratory Reference	Time Point	Storage Condition	Known Related Substances (%)						Total Known Substances (%)	Total Unknown Substances (%)	Total Related Substances (%)
				THN5076	THN5077	THN67003A	THN67003B	THN67003C	THN75083			
Morphine-6- glucuronide phosphate	299620	Initial		ND	ND	0.04	0.04	0.75	0.07	0.86	0.00	0.86
	307567	1 month	25°C/60%RH	ND	ND	0.04	0.04	0.78	0.03	0.85	0.56	1.41
	318592	3 months		0.03	0.07	0.16	0.16	0.78	0.19	1.23	1.08	2.31
	307574	1 month	40°C/75%RH	ND	ND	0.53	0.53	0.70	0.14	1.37	2.07	3.44
	318599	3 months		0.12	0.32	0.75	0.75	0.59	0.06	1.84	4.15	5.99
	307582	1 month	60°C	0.03	0.18	0.90	0.90	0.70	0.27	2.08	3.35	5.43
Morphine-6- glucuronide base	299622	Initial		ND	ND	0.05	0.05	0.87	0.06	0.98	0.00	0.98
	307566	1 month	25°C/60%RH	ND	ND	ND	ND	0.88	0.05	0.93	0.07	1.00
	318593	3 months		ND	ND	0.04	0.04	0.86	ND	0.90	0.52	1.42
	307573	1 month	40°C/75%RH	ND	ND	0.05	0.05	0.85	0.03	0.93	0.34	1.27
	318600	3 months		0.01	0.07	0.23	0.23	0.95	ND	1.26	3.08	4.34
	307580	1 month	60°C	ND	ND	0.19	0.19	0.83	0.02	1.04	1.27	2.31

Claims

1. A hydrobromide salt of morphine-6- β -D-glucuronide (M6G.HBr).
- 5 2. A pharmaceutical composition comprising an analgesically effective amount of M6G.HBr together with a pharmaceutically acceptable carrier, excipient, or diluent.
- 10 3. A pharmaceutical composition comprising an amount of M6G.HBr effective for the treatment of breathlessness in a subject with advanced cancer, together with a pharmaceutically acceptable carrier, excipient, or diluent.
- 15 4. M6G.HBr for use as a medicament.
5. Use of M6G.HBr in the manufacture of a medicament for the treatment of pain.
- 20 6. Use according to claim 5 for the treatment of moderate to severe pain in acute or chronic conditions.
7. Use of M6G.HBr in the manufacture of a medicament for the treatment of breathlessness in a subject with advanced cancer.
- 25 8. A method of treating pain which comprises administering a subject with an analgesically effective amount of M6G.HBr.
9. A method of treating breathlessness in a subject with advanced cancer which comprises administering the subject with an amount of M6G.HBr which is effective for reducing breathlessness.
- 30 10. A method of making M6G.HBr which comprises:
 - 35 (i) contacting a hydrogen bromide solution with a solution of M6G in methanol;

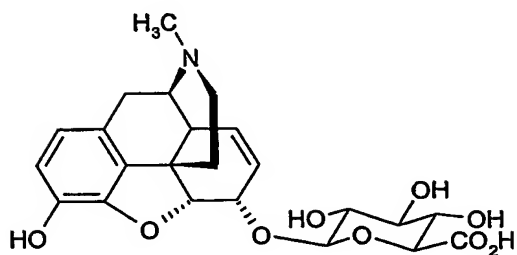
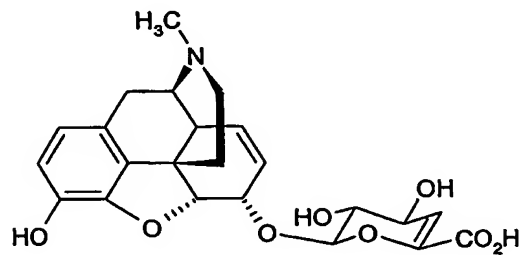
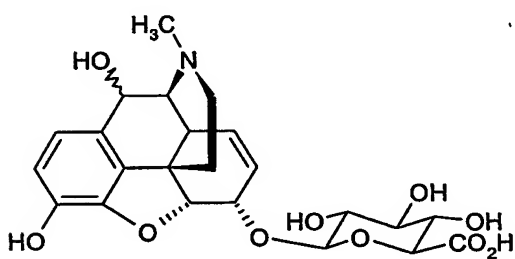
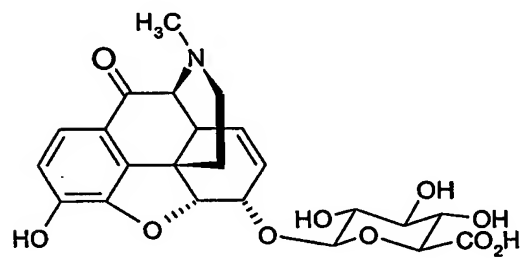
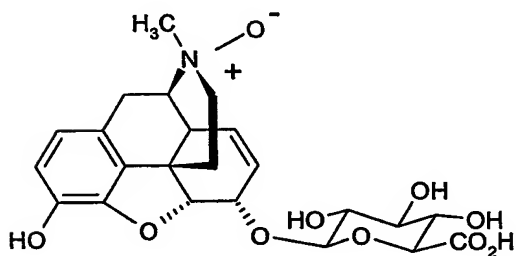
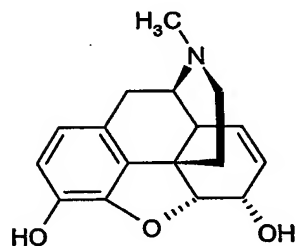
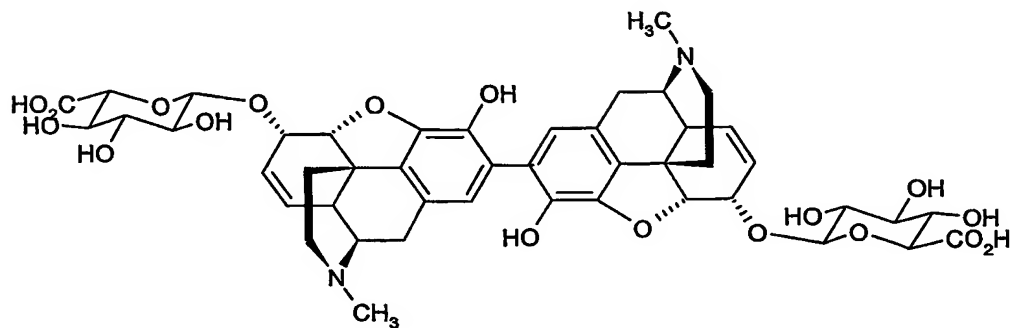
(ii) contacting the solution resulting from step (i) with an organic solvent to precipitate M6G.HBr; and
(iii) isolating M6G.HBr precipitated in step (ii).

5 11. A method according to claim 10, in which the solutions and solvent are at -15°C, or below.

10 12. A method according to claim 10 or 11, which further comprises washing the precipitated M6G.HBr to minimise the amount of organic solvent present.

13. A method according to claim 12, in which the precipitated M6G.HBr is washed with diethyl ether.

15 14. A method according to any of claims 10 to 13, in which the organic solvent of step (ii) is 2-propanol.

Figure 1 Structure of M6G and Identified Related Substances**Morphine-6-β-D-glucuronide (M6G)****HN-33177****HN-67002****HN-67003****HN-75076****Morphine****HN-75083**

INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/GB 03/03562

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H17/00 A61K31/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 816 375 A (ROLABO SL) 7 January 1998 (1998-01-07) page 18	
A	WO 95 20966 A (LOHMANN THERAPIE SYST LTS ;HILLE THOMAS (DE); OTTO KARLHEINZ (DE)) 10 August 1995 (1995-08-10) claim 3	
A	WO 99 15528 A (LOHMANN THERAPIE SYST LTS ;ASMUSSEN BODO (DE); ADAM BERND (DE); HI) 1 April 1999 (1999-04-01)	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the International search

28 November 2003

Date of mailing of the International search report

19/12/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bardili, W

INTERNATIONAL SEARCH REPORT

Inten XXXXXXXXXX cation No
PCT/GB 03/03562

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0816375	A	07-01-1998	EP 0816375 A1	07-01-1998
			JP 10513485 T	22-12-1998
			CA 2211596 A1	19-06-1997
			WO 9721416 A2	19-06-1997
WO 9520966	A	10-08-1995	DE 4403709 A1	10-08-1995
			AT 234096 T	15-03-2003
			CA 2182812 A1	10-08-1995
			DE 59510583 D1	17-04-2003
			DK 742716 T3	16-06-2003
			WO 9520966 A1	10-08-1995
			EP 0742716 A1	20-11-1996
			JP 9509154 T	16-09-1997
			PT 742716 T	31-07-2003
			US 5705186 A	06-01-1998
WO 9915528	A	01-04-1999	DE 19834005 A1	01-04-1999
			AT 214702 T	15-04-2002
			AU 741434 B2	29-11-2001
			AU 9266698 A	12-04-1999
			CA 2304722 A1	01-04-1999
			DE 59803461 D1	25-04-2002
			DK 1017696 T3	08-07-2002
			WO 9915528 A1	01-04-1999
			EP 1017696 A1	12-07-2000
			ES 2174490 T3	01-11-2002
			HU 0003686 A2	28-09-2001
			JP 2001517669 T	09-10-2001
			NO 20001465 A	21-03-2000
			NZ 503459 A	21-12-2001
			PL 339516 A1	18-12-2000
			PT 1017696 T	30-09-2002
			SI 1017696 T1	31-08-2002
			SK 4322000 A3	09-10-2000
			TR 200000653 T2	21-07-2000
			ZA 9808710 A	01-04-1999